

REMARKS

Claims 120-193 are pending in the present application. Applicants thank the Examiner for acknowledging entry of the amendments submitted on October 1, 2009, as indicated on the Advisory Action of November 24, 2009. See Advisory Action, Form PTOL-303, item number 7.

Applicants request reconsideration of the application in view of the following deficiencies in the Advisory Action as received from the PTO:

1. The Advisory Action alleges that applicants' reply to the Final Office Action was filed on October 12, 2009. See Advisory Action, Form PTOL-303, line preceding item number 1. This allegation by the PTO is factually incorrect. Applicants submitted the response to the Final Office Action on October 1, 2009.

2. The Advisory Action fails to acknowledge applicants' timely submission of a Notice of Appeal. See Advisory Action, Form PTOL-303, item number 2, for which the box is not checked and the date has been left blank. This omission on the part of the PTO is factually incorrect. Applicants submitted a Notice of Appeal that was made part of the record on October 15, 2009.

3. The Advisory Action alleges that "Applicants' amendments filed 12 October 2009 have been fully considered but they are not persuasive because *there is nothing in record* the (*sic*) clearly teaches that the antioxidant compound of the prior art references cited do (*sic*) not have the properties recited by Applicants." See Advisory Action, Form PTOL-303, item number 11 (emphasis added). This allegation by the PTO is factually wrong because the applicants explicitly pointed out, in the response submitted on October 1, 2009, that data presented in Table 2 of the application as originally filed clearly show that the exact antioxidant compound of the prior art reference does **not** have the properties of the compounds that are currently claimed, which properties **are** presented in Table 6 of the application as originally filed.

Specifically, in their current form claims 120, 135, 153, 169, 186-188, 192 and 193 expressly recite "wherein the (antioxidant) compound exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity", support for which can be found in the

specification, for example, at page 81, lines 16-17 and Table 6, to distinguish the presently claimed chemically stable antioxidant compound over the prior art bromide salt of U.S. Pat. No. 6,331,532 (Murphy et al.) and its related continuation, U.S. Pat. No. 7,232,809. Decomposition data for the bromide salt of Murphy et al. are shown in the present application, for instance, in Table 2 at page 77, line 28 through page 78, line 3. It is therefore clear that the prior art bromide salts that are characterized in Table 2 do not exhibit “less than 10% decomposition after 60 days at 25°C, 50% relative humidity”, which is a property of the presently claimed subject matter.

Applicants previously pointed out that the instant specification is rife with disclosure teaching this novel and nonobvious feature (*e.g.*, page 3, lines 17-19; page 4, line 13 through page 5, line 2; page 35, lines 3-18; page 36, lines 3-11).

4. The Advisory Action alleges that applicants’ previously filed response was “fully considered” but the PTO fails in any way to address applicants’ repeated requests for clarification as to why two obviousness-type double patenting (ODP) rejections and one statutory double patenting rejection asserted by the PTO over incontrovertibly co-pending applications were not made as provisional double patenting rejections, which is the proper form when the cited applications are still pending, for reasons given below and also previously submitted by applicants.

With regard to a Final Rejection, M.P.E.P. §706.07 notes that the examiner “should never lose sight of the fact that in every case the applicant is entitled to a *full and fair hearing*, and that a clear issue between applicant and examiner should be developed.” (emphasis added). It is respectfully submitted that in view of the objective factual deficiencies enumerated above and elaborated upon below, and for reasons previously made of record in this application, it is not clear that the present application has been “fully considered”, nor that applicants have received a “full and fair hearing”.

Reconsideration of the present application, especially in view of the amendments submitted on October 1, 2009, which have been entered into the record, is now respectfully requested.

REJECTIONS FOR NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

A. The PTO maintains the rejections of claims 120-185, 192 and 193 for alleged non-statutory obviousness-type double patenting over claims 1-10 of U.S. Patent 7,232,809 (Murphy et al.). In particular, the Examiner alleges that the “criticality” of the recited anions to the improved properties of the antioxidant compounds has not been shown.

Applicants respectfully traverse these grounds for rejection. The instant embodiments are directed in pertinent part to a chemically stable antioxidant compound comprising a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety; and an anionic complement for said cationic moiety, wherein the cationic moiety is capable of mitochondrially targeting the antioxidant moiety, wherein the anionic complement is a pharmaceutically acceptable anion that is not a halogen ion or a nitrate anion and is selected from an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate, and does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety, and wherein the antioxidant compound exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity.

For reasons given herein and previously made of record, including in the application as originally filed and in applicants’ response of December 22, 2008, the presently claimed subject matter relates to patentably distinct species. Only in the present application is the problem of instability of the subject lipophilic cation-linked antioxidants disclosed for the first time, including the unexpected finding that bromide salts of the antioxidant compounds made according to U.S. Patent 7,232,809 (which is a continuation of U.S. 6,331,532) are disadvantageously unstable (*e.g.*, present specification at page 3, line 8 through page 5, line 9; Example 7 at pages 73-79). Further, only in the present application is it disclosed for the first time that this problem can surprisingly be overcome, by the use of a non-halogen, non-nitrate, non-reactive pharmaceutically acceptable anion, as taught by the specification (*e.g.*, at page 35, lines 3-18; page 36, lines 3-11; page 3, lines 17-19; page 4, line 13 through page 5, line 2; Examples 8-10 at pages 79-87) and recited by the instant claims.

The present application also discloses unpredicted and unforeseen advantages of the presently claimed antioxidant compounds over those claimed in U.S. 7,232,809, by presenting stability data showing that the present compounds unexpectedly exhibited less than 10% decomposition after 60 days at 25°C, 50% relative humidity (*e.g.*, instant specification at page 81, lines 16-23 and Table 6), *i.e.*, under comparable conditions they were stable for over four times as long as compounds encompassed by the claims of U.S. 7,232,809 (*e.g.*, instant specification at page 77, Table 2).

As applicants have also previously pointed out (Response of December 22, 2008), the present application presents *in vivo* data showing that, unlike the instability exhibited by bromide salts of the prior art (discussed at, *e.g.*, page 3, line 8 through page 5, line 9), the instant compounds exhibited significant pharmacokinetic stability with appreciable concentrations persisting in the circulation 24 hours after intravenous or oral administration (*e.g.*, Example 11 at pages 86-91; see also Figure 31 and Table 12). The previously unforeseen advantages of the presently claimed subject matter for pharmaceutical uses are thus clearly disclosed in the instant application and could not have been predicted by the person having ordinary skill in the art, absent the teachings of the present application. The Examiner therefore errs in asserting that no patentable distinction has been demonstrated.

In the present case, the appropriate test for non-statutory obviousness-type double patenting is whether the invention defined in the instant claims would have been an obvious variation of the invention defined in one or more of claims 1-10 of U.S. 7,232,809. See M.P.E.P. §804(II)(B)(1)(a). In order to establish *prima facie* obviousness, the PTO must identify a reason why a chemist would have been led to modify a compound of U.S. 7,232,809 in the particular manner that would result in the subject matter encompassed by the instant claims, *e.g.*, that comprises one of the expressly recited anionic complements *and* that exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity. See *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 90 USPQ2d 1947, 1951 (Fed. Cir. 2009), citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.* 492 F3d 1350, 1356-57, 83 USPQ2d 1169 (Fed. Cir. 2007). The PTO fails to meet this burden.

In the current Advisory Action, in the Final Office Action of April 15, 2009, and also in the earlier Action of August 5, 2008, the PTO fails to articulate any such reasoning as to why the skilled person would have been led by the prior art to the presently claimed subject matter, nor has the Examiner even been able to point to any identification in the prior art of the problem of poor compound stability for the instant class of compounds, which problem is overcome by the presently claimed subject matter. Even assuming, *arguendo*, that the PTO were to rely on the assertion in the August 5, 2008, Action (at page 9) that the person having ordinary skill in the art were “to form the purpose of achieving acceptable an (*sic*) antioxidant compound”, applicants hasten to point out that this mere allegation lacks evidentiary basis as to why U.S. 7,232,809 would lead such a skilled artisan to use, from amongst myriad possible species that might be available for use as the anionic complement, the presently recited species of an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate.

Moreover, the PTO fails to provide evidence or reasoning as to why the skilled person would, with the requisite reasonable expectation of success, have been able to select an anion that *predictably* would provide an antioxidant compound that “exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity.” Applicants therefore respectfully submit that the presently recited subject matter could not reasonably have been predicted by the claims of U.S. 7,232,809, nor by any specification support for the claims in U.S. 7,232,809 (see M.P.E.P. §804(II)[B](1). “Any obviousness-type double patenting rejection should make clear (A) The differences between the inventions defined by the conflicting claims – a claim in the patent compared to a claim in the application; and (B) The *reasons why* a person of ordinary skill in the art would conclude that the invention defined in the claim at issue would have been an obvious variation of the invention defined in a claim in the patent.” (emphasis added)).

According to the Court of Appeals for the Federal Circuit, unexpectedly improved properties can further rebut an allegation of obviousness. *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 90 USPQ2d at 1952. It is submitted that the presently encompassed subject matter is directed to antioxidant compounds having such unexpectedly improved

properties that could not reasonably have been predicted from the cited patent, and therefore that the instant claims are patentably nonobvious over the claims of U.S. 7,232,809. Reconsideration and withdrawal of the rejection for nonstatutory obviousness-type double patenting are therefore respectfully requested.

B. Claims 120-185 and 192 stand rejected for non-statutory obviousness-type double patenting over claims 120, 122-128 and 130-133 of co-pending application number 11/355,518 and over claims 88-112 of co-pending application number 10/568,654 .

Applicants traverse these grounds of rejection and submit that the subject matter encompassed by the instant claims is patentably distinct over the cited co-pending applications, including for reasons given above and previously made of record.

As a first matter, applicants are confused by the assertion in the Office Action of April 15, 2009, that applicants' argument and amendments filed 22 December 2008 have been "fully considered". In particular, clarification is respectfully requested where it would appear that only a *provisional* double patenting rejection is appropriate here. It is not at all clear that applicants' previous efforts to point out the appropriateness of a *provisional* double patenting rejection have been "fully considered" insofar as in the Office Action of April 15, 2009, the PTO is silent with respect to whether the present rejection is a *provisional* rejection.

On this point, it is submitted that the two applications cited in the present obviousness-type double patenting rejections are co-pending applications. Accordingly, and as applicants explicitly stated in the response of December 22, 2008, because the cited applications are co-pending, at most the PTO can assert a provisional double patenting rejection, which may be maintained in each application:

as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in at least one of the applications. M.P.E.P. § 804(I)(B).

It is therefore submitted that appropriate action can be taken by applicants at such time as the provisional double patenting rejection is the *only* remaining issue. The Examiner is urged to confirm that the present nonstatutory obviousness-type double patenting (ODP) rejections over claims 120, 122-128 and 130-133 of co-pending application number 11/355,518

and over claims 88-112 of co-pending application number 10/568,654 are provisional ODP rejections, or to otherwise explain why they are not.

Moreover, the subject matter of the instant claims is patentably distinct over the claims of the cited co-pending applications for reasons also given above, including the failure by the PTO to provide evidence or reasoning as to why, in the absence of the teachings of the present application, a person having ordinary skill in the art would have been led to an obvious variation of the subject matter of the cited co-pending claims. More specifically, the PTO fails to explain how, from the cited claims of the co-pending applications, the skilled person would have predicted the instant antioxidant compound that exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity and that comprises an anionic complement as recited, with the requisite reasonable expectation of success. As such, applicants submit the present claims are not in conflict with the cited claims of the cited co-pending applications, and no case of ODP is present.

Accordingly and in view of the foregoing, it is therefore submitted that the subject matter of the instant claims is patentably distinct over that of the cited co-pending applications. Reconsideration and withdrawal of the rejections are therefore respectfully requested.

C. The PTO rejects claim 134 under 35 U.S.C. §101 for alleged double patenting over claim 134 of co-pending application number 11/355,518 .

The rejection is traversed. As a first matter, in view of the amendments entered on December 22, 2008, and further upon entry of the amendments submitted on October 1, 2009 (now of record), and particularly in view of the dependency of instant claim 134 on base claim 120, it is submitted that instant claim 134 does not read on claim 134 of the cited co-pending application. As also discussed above, it is respectfully submitted that contrary to the assertion found in the Action, applicants' response of December 22, 2008, has not been "fully considered" where the Action is silent on the question of whether this rejection should properly be a *provisional* rejection because the cited claim is currently pending in a co-pending application.

Applicants believe that because Application No. 11/355,518 remains co-pending to the best of applicants' knowledge at this time, a provisional double patent rejection is

appropriate. According to M.P.E.P. § 804(II)(A), if the conflicting claims are in another co-pending application, form paragraph 8.31 (“*Rejection, 35 U.S.C. 101, Double Patenting*”) should not be used, and instead a provisional double patenting rejection should be made using form paragraph 8.32.

Believing that at most a provisional double patenting rejection may be appropriate here, given applicants’ belief that Application No. 11/355,518 remains co-pending, it is applicants’ understanding that such a provisional double patenting rejection may be maintained in each application “as long as there are conflicting claims in more than one application unless that ‘provisional’ double patenting rejection is the only rejection remaining in at least one of the applications”. M.P.E.P. § 804(I)(B). At such time as this provisional double patenting rejection is the *only* rejection remaining in the present application, appropriate action will be taken. Clarification is respectfully requested if the Examiner believes a provisional double patenting rejection is not appropriate with respect to instant claim 134 in view of claim 134 of co-pending Application No. 11/355,518.

REJECTIONS UNDER 35 U.S.C. § 103

The PTO rejects claims 120-193 under 35 U.S.C. §103 for alleged obviousness over Murphy et al. (U.S. 6,331,532, “the ‘532 patent”). Specifically, the PTO alleges that the ‘532 patent broadly discloses an antioxidant moiety coupled to a lipophilic cation, in complex with an anion that is described *generically*, and concedes that the instant claims are directed more narrowly to such complexes having *specific* anionic species as expressly recited. The Examiner asserts that the ‘532 patent would have motivated the skilled person to make and use the claimed subject matter with a reasonable expectation of success “by evaluating different compounds employed as an (*sic*) that are commercially available to produce a chemically stable antioxidant compound of choice” (Action of April 15, 2009, at page 6).

Applicants respectfully traverse these grounds for rejection. Contrary to the allegations found in the Action (April 15, 2009), the ‘532 patent fails to teach *or suggest* the features of the instant embodiments, which are directed in pertinent part to a chemically stable antioxidant compound comprising a lipophilic cationic moiety linked by a linking moiety to an

antioxidant moiety; and an anionic complement for said cationic moiety, wherein the cationic moiety is capable of mitochondrially targeting the antioxidant moiety, wherein the anionic complement is a pharmaceutically acceptable anion that is not a halogen ion or a nitrate anion and is selected from an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate, and does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety, and wherein the antioxidant compound exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity.

In addition to reasons discussed above and previously made of record in support of the nonobviousness of the claimed subject matter, it is submitted that problems associated with instability of antioxidant compounds prepared according to the teachings of the '532 patent were not recognized prior to the instant application, nor has the PTO presented any evidence to the contrary. Furthermore, the PTO also fails to present evidence that there was any suggestion in the prior art attributing such instability to the choice of anionic complement. Further still, the PTO fails to point to any prior art teaching that could have suggested which of the many possible anions should be used to obtain a stable product. As such, the PTO impermissibly employs hindsight in its allegation under "rational (*sic*) and motivation" (Action of April 15, 2009, bottom of page 5 through first two paragraphs of page 6) that the skilled person would have been motivated by the '532 patent to arrive at the presently claimed chemically stable antioxidant compound. The PTO further fails to establish that the '532 patent would have suggested the presently claimed subject matter to the skilled person with the *requisite* reasonable expectation of success.

It is axiomatic that obviousness is determined with respect to the claimed subject matter as a whole, and not to separate parts of the claim. *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). A proper analysis of the instant claims therefore should not be limited to consideration of the presently recited anions in isolation (Action of April 15, 2009, page 5, last paragraph), but should instead be an analysis of the full scope of subject matter encompassed by the claim as a whole. Furthermore, the use of hindsight is inappropriate where teachings of the claimed invention are improperly read into the prior art. *KSR*, at 1742.

Here, the PTO points to no evidence whatsoever that the problem of poor stability had even been recognized for antioxidant compounds made according to the '532 patent, nor does the PTO point to any suggestion in the prior art regarding how predictably to improve the stability of such compounds. Hence, the PTO fails to support its allegation that the "instantly claimed chemically stable antioxidant compound . . . would have been suggested to one of ordinary skill in view of the teachings of the prior art reference cited." (Action of April 15, 2009, page 6, lines 1-3). For reasons given herein, the prior art nowhere suggests to the person having ordinary skill that, in the context of the instant claim as a whole, any of the presently recited pharmaceutically acceptable anions could reasonably be expected to confer the recited properties (e.g., "does not exhibit reactivity . . .", "exhibits less than 10% decomposition. . .") on the encompassed antioxidant compounds.

Applicants therefore respectfully submit that the PTO fails to establish *prima facie* obviousness where it fails to meet its burden of showing that all of the claimed elements were known in the prior art, that a person skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and that the combination would have yielded nothing more than predictable results to such a skilled person. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385. Additionally, the PTO fails to meet its burden of showing that the person skilled in the art would have had a reasonable expectation of success in arriving at the claimed subject matter. M.P.E.P. § 2143.02 (citing *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986)).

Accordingly and as discussed above, it is submitted that the PTO fails to provide evidence or reasoning as to why the skilled person would reasonably have expected *successfully* to combine the recited elements. By alleging otherwise, the PTO impermissibly employs hindsight in view of the present application. "A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 127 S.Ct. 1727, 82 USPQ2d 1385, 1395 (2007), No. 04-1350 4, 14, (U.S. April 30, 2007).

In view of the foregoing, reconsideration of the application and an indication of the allowability of the claims are therefore respectfully requested. Should the Examiner believe that any issues remain outstanding in the present application, it is urged that a telephone inquiry please be made to the applicants' undersigned representative at the Examiner's earliest possible convenience.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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